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Alpha oscillations are causally linked to inhibitory abilities in ageing.

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ABSTRACT

Ageing adults typically show reduced ability to ignore task-irrelevant information, an essential skill for optimal performance in many cognitive operations, including those requiring working memory (WM) resources. In a first experiment, young and elderly human participants of both genders performed an established WM paradigm probing inhibitory abilities by means of valid, invalid and neutral retro-cues. Elderly participants showed an overall cost, especially in performing invalid trials while youngers' general performance was comparatively higher, as expected.

Inhibitory abilities have been linked to alpha brain oscillations but it is yet unknown whether in ageing these oscillations (also typically impoverished) and inhibitory abilities are causally-linked. To probe this possible causal link in ageing, we compared in a second experiment parietal alpha-transcranial alternating current stimulation (tACS) with either no stimulation (Sham) or with two control stimulation frequencies (theta- and gamma-tACS) in the elderly group while performing the same WM paradigm. Alpha- (but not theta- or gamma-) tACS selectively and significantly improved performance (now comparable to younger adults' performance in the first experiment), particularly for invalid cues where initially elderly showed the highest costs. Alpha oscillations are therefore causally linked to inhibitory abilities and frequency-tuned alpha-tACS interventions can selectively change these abilities in the elderly.

SIGNIFICANT STATEMENT

Ignoring task-irrelevant information, an ability associated to rhythmic brain activity in the alpha frequency band, is fundamental for optimal performance. Indeed, impoverished inhibitory abilities contribute to age-related decline in cognitive functions like working memory (WM), the capacity to briefly hold information in mind. Whether in ageing adults alpha oscillations and inhibitory abilities are *causally* linked is yet unknown.

We experimentally manipulated frequency-tuned brain activity using transcranial alternating current stimulation (tACS), combined with a retro-cue paradigm assessing WM and inhibition. We found that alpha-tACS induced a significant improvement in target responses and misbinding errors –two indexes of inhibition. We concluded that in ageing alpha oscillations are causally linked to inhibitory abilities, and that despite being impoverished, these abilities are still malleable.

INTRODUCTION

The ability to ignore information that is irrelevant for a given cognitive activity is fundamental for optimal performance (Gazzaley and Nobre, 2012; Hasher and Zacks, 1988). Importantly, impoverished inhibitory abilities are a contributing factor to age-related decline in several cognitive functions including working memory (WM), the capacity to hold information in mind for brief periods of time (Gazzaley et al, 2005; Hasher and Zacks, 1988; Hasher et al, 2007; Salthouse and Meinz, 1995).

Inhibitory abilities have been linked to brain oscillations, i.e. rhythmic brain activity, in the alpha frequency band (8-13 Hz) in the occipito-parietal areas among others (Constantinidis and Klingberg, 2016; Gazzaley and Nobre, 2012; Herrmann et al, 2013; Jensen and Mazaheri, 2010; Klimesch et al, 2007; Rihs et al, 2007; Tuladhar et al, 2007; Thut et al, 2007). Alpha oscillations have been associated to functional inhibition as alpha amplitude has been shown to decrease in task-relevant brain areas and increase in task-irrelevant ones (Foxe and Snyder, 2011; Hanslmayr et al, 2011; Jensen and Mazaheri, 2010; Kelly et al, 2006; Sauseng et al, 2009; Rihs et al, 2009; Thut et al, 2006; Romei et al, 2010; Zanto and Gazzaley, 2009). This is supported by correlational evidence from EEG studies showing that when ongoing alpha amplitude is high, young participants successfully inhibit task-irrelevant stimuli in WM tasks (Klimesch, 1999; Sauseng et al, 2009). Recently, alpha frequency-related physiological and behavioural effects have been induced by experimentally manipulating frequency-tuned brain stimulation in the form of transcranial alternating current stimulation (tACS). This safe technique allows us targeting specific brain oscillations (Antal and Paulus, 2013; Herrmann et al, 2013; Marshall and Binder, 2013; Parkin et al, 2015; Sauseng and Klimesch, 2008; Thut et al, 2011), and possibly modulating cognitive functions relying on these oscillations (Basar et al, 2001; Cecere et al, 2015; Engel et al, 2001; Helfrich et al, 2014; Herrmann et al, 2004). For instance, in young participants alpha-tACS increases endogenous alpha activity in parieto-occipital areas (Zaehle et al, 2010), and modulates target detection performance (Helfrich et al, 2014).

The age-related reduction of alpha amplitude (Klimesch, 1999; Klimesch et al, 2007; Vaden et al, 2012) and the age-associated weakening of inhibitory abilities purportedly associated with such oscillations (Craik and Salthouse, 2000; Gazzaley et al, 2005, 2008; Hasher and Zacks, 1988; Hasher et al, 2007; McEvoy et al, 2001; Salthouse and Meinz, 1995) may suggest a causal link between inhibitory processes and alpha oscillations. To test whether such link exists, we adapted an established WM paradigm which provides an index of WM precision, and of the source of error in performance including indexes of inhibitory abilities (Bays and Husain, 2008; Bays et al, 2011; Gorgoraptis et al, 2011; Ma et al, 2014; Pertzov et al, 2013). During the WM maintenance interval, we used probabilistic retrospective cues (retro-cues) triggering top-down biasing mechanisms which prioritize a maintained stimulus in WM (Berryhill et al, 2012; Gazzaley and Nobre, 2012; Gozenmann et al, 2014; Griffin and Nobre, 2003; Landman et al, 2003; Makovski and Jiang, 2007; Makovski et al, 2008; Matsukura et al, 2007; Mok et al, 2016; Pertzov et al, 2013; Rerko and Oberauer, 2013; Tanoue and Berryhill, 2012). Crucially, some of these retro-cues (invalid retro-cues) prioritize information that will not subsequently be recalled, and therefore need a stronger suppression of task-irrelevant information at retrieval stage, a process that in younger adults typically results in reduced accuracy relative to other retro-cues (Astle et al, 2012; Griffin and Nobre, 2003; Matsukura et al, 2007; Pertzov et al, 2013). By combining this retro-cue paradigm with parietal alpha-tACS we reasoned that if inhibitory abilities are linked to alpha oscillations in the ageing brain, then alpha-tACS may modulate ageing participants' impoverished endogenous alpha amplitude, which may in turn impact on inhibitory abilities and ameliorate WM performance. Alternatively, no changes in inhibitory abilities by alpha-tACS may suggest that any link between alpha oscillations and declined inhibitory abilities is just mediated by age.

METHODS

Participants

Fifty right-handed, stimulation-compatible (Antal & Paulus, 2013; Tavakoli &, Yun, 2017) subjects with normal or corrected vision provided written consent to participate in our double-blind experiment that was approved by the local Ethics Committee. Twenty-five of them were elderly (14 males; mean age= 69.1± 4.5 years; age range= 62-78; education: mean= 16.2±4 years; range=13-22) and twenty-five were younger (11 males; mean age= 24.8±4.3 years; age range= 18-33; education: mean= 15.2±5 years; range=14-20). Younger adults performed the same experimental task as the elderly adults in the absence of tAC stimulation for comparative purposes (Experiment 1, see below). A future study will investigate young participants' performance with an equivalent tACS-based study.

All participants were assessed for colour blindness and none of them showed impairment in colour perception. Moreover, none of the participants had past history of neurological or psychiatric disorders, was under regular medication, or showed major cognitive impairments assessed with the Mini Mental State Examination (MMSE, Folstein et al, 1975; for elderly participants only). Subjects received a monetary compensation to complete the experiment. The same elderly participants took part in Experiments 1 and 2, and a subgroup of them took part in Experiment 3.

Experimental design and task

The same retro-cue WM paradigm was used in the first and second experiment, where we tested, respectively, for any differential performance between young and elderly adults, and for the possible causal link between alpha oscillations and inhibitory abilities in our ageing sample only. Our paradigm is more complex than simpler WM tasks such as the digit or letter span, but was purposely chosen because: (1) it provides a continuous rather than a binary measure of WM performance, which allows better measuring of the fidelity or quality of WM representations (Alvarez & Cavanagh, 2004; Bays et al, 2009; Bays & Husain, 2008; Ma et al, 2014); (2) it measures WM accuracy as well as the source of errors, and (3) some of

these errors, specifically the probability of target responses and misbinding, provide a measure of inhibitory processes which is the focus of our investigation.

Participants memorized a 1000 ms display of four arrow stimuli (visual angle: 2° x 0.3°) differing in colour and orientation. The arrows were simultaneously presented to the left and right (two for each side) of a black, 0.8° diameter fixation cross. Within a trial, they appeared in four out of five randomly selected and easily distinguishable colours (yellow, red, blue, green and white), and were arbitrarily oriented with a minimum of 10° difference between the stimuli. Participants were asked to keep in mind both the orientation and colour of these arrows. Memory array was followed by a 1000ms delay during which a retro-cue may or may not have been presented (100ms). A 3000ms delay period preceded the presentation of one of the four coloured arrows (the probe) which reappeared in a random orientation. Participants used a continuous, analogue response to match it as closely as possible to the original orientation (see also Pertzov et al, 2013; Figure 1).

In Experiment 1 and 2, 30% of trials (*N*=42) had the memory delay filled by a fixation cross that remained black, i.e. a *neutral condition*. In the remaining 70% of trials, a 100 ms retro-cue was presented 1000 ms after the presentation of the memory array. The retro-cue indicated the colour of the stimulus arrow most likely to be later probed. In 70% of these retro-cue trials (*N*=56), the cue corresponded to the item that was subsequently probed (*valid condition*). The remaining 30% of the retro-cue trials (*N*=28) cued an item that was not subsequently probed (*invalid condition*). In Experiment 3, which aimed to test whether retro-cues may act as distracters, 30% of the trials (*N*=42) consisted of a neutral condition equivalent to the one used in Experiments 1 and 2. In the remaining 70% of the trials (*N*=84) the colour of the fixation changed into a colour that was never part of the stimulus display, i.e. pink (*task-irrelevant cueing condition*).

In all experiments, participants were seated in front of a 21" CRT monitor at a viewing distance of 60 cm. Testing sessions were conducted in a darkened and soundproof room; in order to maintain a stable visual field, a chin rest supported participants' head. Tasks were programmed in Matlab 7.0 using the Cogent toolbox (http://www.mathworks.co.uk). Each testing session lasted about one hour.

Figure 1

Using an established probabilistic model, the retro-cue WM paradigm assesses general WM precision, and quantifies the contribution of separate sources of error to performance (see Bays and Husain, 2008; Bays et al, 2011; Gorgoraptis et al, 2011; Ma et al, 2014; Pertzov et al, 2013). Specifically, errors were in terms of the noisiness of memory for the target item, the probability of responding to the target, to a non-target, and of responding at random (guessing). Noisiness of memory or increase in variability of memory for the target orientation is an indication of how well the memory trace was 'protected' during the retention period. Increase probability to respond to the target orientation is a measure of maintained inhibitory abilities and selective attention. Increase probability to respond to the non-target orientation (non-probed item) is used as a measure of impaired inhibition and selective attention, because observers misbind the colour of the probed item to the orientation of one of the other items in memory. Finally, an increase in random responses, i.e. independent of any orientation in memory, can also contribute to error in performance due to factors such as inattention, distraction, or lack of compliance with the task.

Stimulation design

In Experiment 2, we used the same WM retro-cueing task and data analysis as Experiment 1 to probe the possible causal link between alpha oscillations and inhibitory abilities in our ageing sample. Ageing adults only underwent four experimental sessions at least two days apart; in each session, while performing the same task, they received bilateral parietal tACS stimulation at either 4Hz (**Θ** band), 10Hz (**α** band), 35Hz (**γ** band), or Sham. The order of the stimulation conditions was counterbalanced and pseudo-randomized across participants. Parietal regions were targeted because: (1) they are known for being involved in

inhibitory processes, which are at the core of our investigation (Constantinidis and Klingberg, 2016; Gazzaley and Nobre, 2012; Kelly et al, 2006; Klimesch, 2012); and because (2) they have also been systematically targeted as the main alpha generator, as shown in several M/EEG (Capotosto et al, 2017; Fu et al, 2001; Rhis et al, 2009) and brain stimulation studies (including Romei et al, 2010, 2012; Thut et al, 2012).

We reasoned that if alpha oscillations are causally linked to inhibitory processes, then relative to Sham or to another stimulation frequency (see below) alpha-tACS may enhance inhibitory abilities and attenuate both the inter-stimuli competition at encoding and the effect of the retro-cue. Attenuating this competition may increase inter-stimuli interference (Berryhill et al, 2012; Bonnefond and Jensen, 2013; Desimone and Duncan, 1995). This may in turn impoverish memory recall and increase misbinding errors more strongly in neutral cues where no retro-cue is available to offset the inter-stimuli interference. Moreover, any alpha-tACS induced change in performance may be larger or specific to invalidly-cued trials; in our first experiment these trials led to the largest cost in performance in ageing adults because they require suppressing information that had been invalidly prioritized (see below and Pertzov et al, 2013), hence reducing the effect of retro-cue with alpha-tACS may result in the largest improvements in these invalid trials.

To exclude any generic learning or fatigue effects, Sham stimulation was used in the same ageing participants in a different testing session. Theta-tACS was used as an active stimulation condition, with no significant changes in performance predicted following it. This is because theta oscillations are known to more strongly reflect maintenance of items presented sequentially and with progressively increasing load (Jensen, 2006), two factors that we did not manipulate in our design. We also tested whether gamma-tACS may modulate the precision of memory recall since gamma oscillations are known to reflect changes in encoding or maintaining items in WM, as well as in re-directing attention to internal WM representations (Buzsaki and Wang, 2012; Jensen et al, 2007; Poch et al, 2014; Ray and Maunsell, 2015; Roux et al, 2012; Tallon-Baudry et al, 1999).

In Experiment 3, some of the same ageing participants underwent two experimental sessions each, at least two days apart, based on the same task and procedures as in Experiment 2. However, a variant of the retro-cueing condition described above was used, consisting of including task-irrelevant and neutral cues. Since the results of Experiment 2 indicated significant changes in performance following alpha stimulation relative to Sham (see below), Experiment 3 focused on alpha and Sham parietal stimulation only, which were applied to ageing adults in alternated order.

A sinusoidal stimulation was applied with a MagStim stimulator and delivered through two 35cm^2 (5 x 7 cm) rubber electrodes, each covered with a sponge pad soaked in saline solution and positioned over the subject's scalp. In each session, participants were stimulated at a specific frequency (4, 10 or 35 Hz in Experiment 2; 10 Hz only in Experiment 3, in addition to Sham in all studies) for 20 min with a current strength of 1500 μA (average current density: was ~42.9 μA/cm^2) and a fade in/out period of 20 seconds. To allow successful blinding of participants, during Sham stimulation the same setting was maintained compared to active stimulation, but the current settled at the lowest frequency (i.e. 4 Hz) was turned off after 20 seconds, so that any cutaneous sensation was the same during active and Sham stimulation (e.g. Fertonani et al, 2011; Gandiga et al, 2006).

Based on the standard 10-20 EEG system (Oostenvelt et al, 2001), parietal and Sham stimulation electrodes were placed on the target parietal areas corresponding to P3 and P4, and held in place by means of an elastic band. During the whole time-course of the experiment, participants as well as the experimenter placing the electrodes and running the experimental protocol were not told whether active or Sham stimulation was used in any given session. All ageing participants performed all experiments, and a subgroup of them performed Experiment 3 during parietal theta-tACS. Given the posterior electrode montage none of the participants reported seeing phosphenes.

Figure 2

Statistical Analysis

Recall precision was used as an overall measure of performance, obtained by calculating the angular deviation between the orientation reported by the subject and the orientation of the target arrow in the initial memory display. For each retro-cueing condition, recall precision was defined as the reciprocal of the circular standard deviation of error in response.

Moreover, by applying an established probabilistic model (see Bays and Husain, 2008; Bays et al, 2011), the sources of error underlying performance in the WM retro-cueing task could be deconstructed, and their effect on performance estimated separately. This model is described as follows:

$$p(\hat{\theta}) = a\phi_K(\hat{\theta} - \theta) + \beta \frac{1}{m} \sum_{i}^{m} \phi_K(\hat{\theta} - \varphi_i) + \gamma \frac{1}{2\pi}$$

where θ is the true orientation of the target item, ˆ the orientation reported by the subject, and Φ_κ is the von Mises distribution (the circular analogue of the Gaussian distribution) with mean of zero and concentration parameter κ. Concentration parameter κ reflects the variability of recall of the target feature, whereby higher κ corresponds to lower variability. The probability of reporting the correct target item (pT) is given by α. The probability of misreporting a non-target item (pNT) is given by β, and {φ1, φ2, ...φm} are the orientations of the non-target items. The probability of responding randomly (pU) is given by γ=1-α-β. Maximum likelihood estimates (Myung et al, 2013) of the parameters κ, α, β and γ were obtained separately for each subject, stimulation condition and retro-cue type using an expectation–maximization algorithm.

Performance in absence of stimulation was investigated by fitting repeated measures regressions, using as predictors retro-cueing type (valid, invalid and neutral) and either age group (young and older) for Experiment 1, or stimulation condition (Sham, Alpha and Gamma) in Experiment 2. For this experiment, the same analysis was repeated also including performance of the subgroup of participants who received theta-tACS.

The Generalized Estimating Equations (GEE) procedure legitimates the analysis of data violating the normality assumption, as in the case of the current data. Accuracy (precision) and each index of error (pT, pNT, Kappa, pU) were separately modeled through gamma regression with a loglog link function. Significant main effects or interactions were followed by GEE-based t-tests with the least-significant difference test correction for multiple comparisons (see Santernecchi et al, 2013 for a similar approach).

Across all performance indexes and stimulation conditions, 9 data points for the ageing adults (0.6%), and 6 for the younger sample (1.6%) were disregarded because of poor model fitting. An additional 9 (0.6%) and 3 (0.8%) data points which were over 3 standard deviations from the group mean were excluded from the analyses of the older and younger adults' performance respectively.

RESULTS

Experiment 1

Working memory retro-cueing task in younger and ageing adults

Overall performance – recall precision

The fidelity with which the probe was recalled was significantly more precise in younger than older adults across cueing conditions (χ^2 =14.5, p<0.001), a large difference (Cohen's d=1.05) based on Cohen's criteria (Cohen, 1988). Moreover, in the two age groups, precision was differently modulated by cue type (significant interaction of retro-cue type and age group, χ^2 =6.6, p=0.03), because it was significantly greater in valid trials in younger relative to older adults (mean difference = -0.27, p<0.001 corrected), a large between-group difference (Cohen's d=1.12). In ageing compared to younger participants precision was also significantly lower in invalid and neutral trials (respectively, mean difference = -0.22, p=0.03, and -0.18, p<0.01 corrected; Cohen's d=0.82 and 0.82), see Table 1.

In younger adults, recall precision was significantly greater for valid relative to neutral trials (mean difference = 0.06, p=0.04 corrected; Cohen's d=0.24). No other effects reached significance.

Inhibitory abilities – Probability to respond to the target orientation (pT)

Regardless of cue type, the probability of responding to the target orientation was higher in younger relative to older participants (χ^2 =9.5, p=0.002), a large group difference (Cohen's d=0.92). Moreover, target responses were influenced by cue type in both younger and older participants (χ^2 =13.2, p=0.001), because performance was worse in invalid trials (0.65, SE: 0.06) relative to valid (0.80, SE: 0.06; mean difference = -0.155, p<0.001 corrected) and to neutral ones (0.78, SE: 0.04; mean difference = -0.13, p=0.002 corrected).

As well as by cue type, target responses were also significantly influenced by their combination with age group (interaction retro-cue and group, χ^2 =8.05, p<0.02), because there was an advantage for younger relative to older participants in valid trials (mean difference = -0.14, p=0.002 corrected; Cohen's d=0.86), and a larger cost for older relative to younger participants in invalid ones (mean difference = -0.21, p=0.002 corrected; Cohen's d=0.86). Remarkably, in absence of retro-cue (neutral cue), performance was equivalent in the two age groups (p=0.9). This is supported by the Bayesian factor (BF_{01}=.35), obtained by running a Bayesian analysis on the *JASP* platform (Version 0.8.2, JASP Team, Wagenmakers et al, 2017) with default (Cauchy) prior, which suggested strong evidence (Rafery, 1995) for the similarity of target responses in the two age groups in trials with neutral retro-cues, see Figure 3A and Table 1.

In the ageing group, the cost associated with invalid trials was significantly higher relative to valid (mean difference = -0.18, p=0.005 corrected; Cohen's d=0.78) and neutral (i.e. uncued) trials (mean difference = -0.23, p<0.001 corrected; Cohen's d=0.90), whereas in younger adults the advantage associated to valid trials was significantly higher than in neutral (mean difference = 0.10, p<0.03 corrected, Cohen's d=0.9) and invalid ones (mean difference = -0.12, p<0.02 corrected, Cohen's d=0.67), see Figure 3A and Table 1.

Inhibitory abilities – Misbinding: Probability of responding to non-target orientations (pNT)

Older adults made significantly more misbinding errors compared to younger participants, regardless of the retro-cueing condition (χ^2 =7.9, p=0.005; Cohen's d=0.79). Across age groups, the occurrence of these errors was also modulated by cue type (χ^2 =9.8, p=0.007), because there were significantly more misbinding errors (worse performance) in invalid relative to valid trials (mean difference = 0.09, p=0.005 corrected; Cohen's d=0.6), see Figure 4A and Table 1. The interaction of cue type and age group did not reach significance.

Noisiness of memory for the target item (Kappa)

The noisiness of memory for the target item did not change in any retro-cueing conditions across age groups (Ps>0.1), see Table 1.

Random error (pU)

No changes in the proportion of random responses were observed in any retro-cueing conditions across age groups (Ps>0.2), see Table 1.

Table 1

Experiment 1 showed that age modulates memory precision as well as two indexes of inhibitory abilities, target responses and misbinding errors. Specifically, memory recall was significantly less precise, the probability of target responses lower and of non-target responses (misbinding errors) higher in ageing adults compared to younger across all retro-cued trials. Moreover, in older relative to younger adults there was also a significantly higher cost in performing invalid trials and a reduced benefit of valid trials in memory recall and target response. Strikingly, in absence of retro-cue (neutral cue), recall precision and target responses did not differ in the two age groups.

This pattern of results first indicates that when not influenced by the retro-cue, ageing adults were as good as younger at responding to targets. Secondly, despite a cost in performance, ageing adults' memory was still modulated by retro-cues, with a significant difference between cue types which

suggests that elderly's memory retained some flexibility. Using parietal tACS in our ageing sample, Experiment 2 tested whether inhibitory abilities –measured in terms of target responses and misbinding errors– as well as memory precision, may be causally linked to specific brain oscillations.

Experiment 2

Working memory retro-cueing task with tACS in ageing adults

Values reflecting accuracy (precision) and the sources of error (pT, pNT, Kappa, pU) in all stimulation conditions are presented in Table 2.

Overall performance – recall precision

Precision values can be influenced by changes in any of the three sources of error, and we did not observe any significant effect of retro-cue type, stimulation condition or their combination on precision at the group level in our regression analysis of the precision data (all *P*s> 0.1). Similar results were obtained when theta-tACS performance was considered (*Ps*>0.4), see Table 2. However, a closer inspection of the data showed a large variability in performance such that about 2 / 3 of the participants showed that the fidelity with which the probe was recalled improved following alpha and gamma-tACS, whereas in the remaining 1 / 3 recall precision did not improve following stimulation. These results therefore suggest that following alpha and gamma-tACS, lack of significant group changes in precision may be because of the large individual variability in elderly's performance in this index.

Inhibitory abilities – Probability to respond to the target orientation (pT)

A further GEE-based regression analysis of the modelling data with tACS conditions and cue type as predictors, shows that, however, stimulation had a marginal significant impact on target responses overall (χ^2=5.5, p=0.06). This is because irrespective of retro-cue type, the probability of responding to the target stimulus was higher following alpha-tACS relative to Gamma (mean difference = 0.066, p<0.03 corrected, Cohen's d=0.51), and marginally to Sham (mean difference=0.046, p=0.07 corrected, Cohen's d=0.46).

Target responses also depended on the specific cueing condition (significant interaction of stimulation and cue type, χ^2=31.1, p<0.001). In all but two ageing adults there was a large (Cohen, 1988) and significant difference in target responses between alpha-tACS and both Sham (mean difference = 0.25, p<0.001 corrected, Cohen's d=1.24) and gamma-tACS (mean difference = 0.16, p=0.001 corrected, Cohen's d=0.82) in trials with invalid retro-cues; see Table 2 and Figure 3B. Similar results were observed when theta-tACS performance was considered (χ^2=27.2, p<0.001), with invalid trials significantly better performed during alpha compared to theta-tACS (mean difference = 0.24, p<0.001 corrected, Cohen's d=0.98). Remarkably, in aging participants target responses in invalid trials following alpha-tACS did not differ from target responses in the same trials in younger participants in the pre-stimulation (baseline) condition. The Bayesian factor (BF_{01} = .25) obtained by running a Bayesian analysis on the *JASP* platform (Version 0.8.2, JASP Team, Wagenmakers et al, 2017) with default (Cauchy) prior, strongly (Rafery, 1995) supported this observation; see Table 2 and Figure 3B. Alpha stimulation therefore successfully restored performance in the elderly. Ageing adults' alpha-tACS target responses in neutral trials also did not differ from target responses in invalid trials in younger adults at baseline. Again, the Bayesian factor (BF_{01} = .31) based on a Bayesian analysis on the *JASP* platform (Version 0.8.2, JASP Team, Wagenmakers et al, 2017) with default (Cauchy) prior, strongly (Rafery, 1995) maintained this conclusion; see Table 2 and Figure 3B.

To examine the extent to which alpha-based improvement in invalid trials was modulated by individual differences in the Sham condition, which served as baseline performance, a correlation analysis was run. This showed that alpha-tACS induced changes depended on the baseline performance (Spearman's rho correlation, r_{24}= -0.82, p<0.001), because older participants with lower probability of target responses at the

start improved the most following alpha-tACS, see Figure 5A. There was also a significant correlation between gamma-tACS target responses and baseline (r_{24}=-0.57, p=0.003); we note however, that because gamma-tACS changes were not significant, interpreting this correlation is difficult. No significant correlation emerged between theta-tACS target responses and baseline (p>0.08).

We also observed marginally significant decreased target responses in neutral trials during alpha-tACS relative to Sham (mean difference = -0.11, p=0.06 corrected, Cohen's d=0.49, see Figure 3B and Table 2). Alpha-driven changes in performing these neutral trials did not significantly correlate with baseline performance. During Sham tACS, the probability of responding to the target stimuli was significantly higher in valid relative to invalid trials (mean difference = 0.17, p<0.001, Cohen's d= 0.88), and showed a trend towards significance relative to neutral trials (mean difference = -0.05, p=0.08, Cohen's d= 0.29). No significant changes in performance were observed following other stimulation or cueing conditions.

Inhibitory abilities – Misbinding: Probability of responding to non-target orientations (pNT)

Further GEE analyses of the modelling data show that stimulation significantly modulated non-target responses depending on the type of retro-cue (interaction of retro-cue and stimulation condition, χ^2=13.8, p<0.01). Specifically, there was a significant change in misbinding errors following alpha stimulation: relative to Sham and gamma stimulation, pNT decreased in invalid trials (mean difference = -0.17, p<0.001, Cohen's d= 0.93, and -0.11, p<0.02, Cohen's d= 0.5 corrected, respectively) and showed a tendency to increase in neutral ones when compared to Sham (mean difference = 0.1, p=0.06 corrected, Cohen's d=0.4), but not gamma-tACS (mean difference= 0.03, p=0.6), see Figure 4B and Table 2. During Sham tACS, the probability to respond to non-target stimuli (misbinding errors, pNT) was significantly higher in invalid relative to valid trials (mean difference = -0.11, p=0.002, Cohen's d= 0.28). No other effects reached significance (all Ps>0.1). Similar results were observed when theta-tACS performance was

considered (χ^2=30.5, p<0.001), with a significant difference between alpha- and theta-tACS performance in misbinding errors (mean difference = 0.14, p<0.02 corrected, Cohen's d=0.52).

To examine the extent to which these alpha-based changes were influenced by baseline performance (Sham condition), a correlation analysis was run. This showed that misbinding errors following alpha-tACS in invalidly-cued trials depended from participants' baseline performance (Spearman's rho correlation, r_{24}= -0.73, p<0.001), because older adults with higher probability of non-target responses in Sham improved the most following alpha-tACS, see Figure 5B. There was also a significant correlation between gamma-tACS misbinding errors and baseline (r_{24}= 0.45, p=0.03); we note however, that because gamma-tACS changes were not significant, definite interpretations of this correlation are difficult. No significant correlation emerged between theta-tACS misbinding errors and baseline (p>0.2).

Noisiness of memory for the target item (Kappa)

No significant changes in performance were observed in any stimulation or retro-cueing conditions (all *P*s>0.1) in ageing adults. The same was found when considering theta-tACS (all *P*s>0.2).

Random error (pU)

No significant changes were observed in the proportion of random responses in any stimulation or retro-cueing conditions in ageing participants (all *P*s>0.3). The same results were found when theta-tACS was taken into account (all *P*s>0.2).

Table 2, Figure 3, Figure 4, Figure 5

Experiment 2 indicated for the first time that alpha-tACS successfully restored performance in ageing adults who showed significantly higher probability to respond to target stimuli (pT) and lower probability of misbinding errors (pNT) relative to Sham, gamma and theta stimulation. These changes may be because alpha-tACS reduced the stimuli competition for attentional and memory resources at encoding, and attenuated the impact of the retro-cue on the probe. Reducing stimuli competition is likely to have increased

the interference among the stimuli, which was especially detrimental for performing neutral trials (i.e. no retro-cue). This is because stimuli interference was not counteracted by any retro-cue, such that no item was prioritized relative to the others, and misbinding errors (pNT) therefore increased. Alpha also attenuated the effect of the retro-cue such that responses were less corrupted by the cued item, an advantage that was particularly strong in invalid trials since pre-stimulation they corresponded to the largest cost in performance and therefore allowed larger improvements. Strikingly, post-alpha the probability of target responses in ageing adults' in invalid trials did not differ from baseline performance in younger adults.

Experiment 3

Working memory retro-cueing task with task-irrelevant retro-cues in ageing adults

The alpha-driven improvement in target responses in ageing participants may be due to reduced stimuli competition and to the attenuation of the retro-cue effect, which especially reduced the impact on performance of the invalidly prioritized item. In ageing, however, retro-cues also act as distractors (Duarte et al, 2013; Newsome et al, 2015), leaving unclear whether alpha may have had a role in suppressing distractors. To assess this, we designed a third experiment using the identical experimental paradigm as Experiments 1 and 2, and with an equally distracting but task-irrelevant retro-cueing condition. This consisted of a retro-cue of a colour that never belonged to the arrow stimuli (pink), and therefore was not intended to modulate response to the target orientation.

The same parameters as in Experiment 1 and 2 reflecting accuracy (precision) and the sources of error (pT, pNT, Kappa, pU) in both stimulation conditions are presented in Table 2. As for the previous analyses, independent regression analyses were run for each value, based on the generalized estimating equation (GEE) with gamma regression and loglog link, with tACS conditions (Sham, Alpha) and retro-cue type (task-irrelevant and neutral) as predictors.

We found no significant change in participants' recall precision in any of the retro-cueing or stimulation conditions (no main effects or interactions, all *P*s>0.09). Likewise, there was no significant change in Kappa (all *P*s>0.27), in the proportion of non-target (pNT, all *P*s>0.2) and random responses (pU, all *P*s>0.36). We also observed no changes in target responses (pT, all *P*s>0.09), with a tendency for lower probability of responding to the target (lower pT, i.e. worse performance) in the context of task-irrelevant compared to neutral retro-cues across stimulation conditions (mean difference = -0.04, p=0.08, corrected), see Figure 6 A and B, Table 2.

These results showed that in absence of stimulation, task-irrelevant retro-cues did not significantly affect ageing adults' performance as task-relevant retro-cues (Experiments 1 and 2) did. We note, however, that although non-significant, the probability of responding to target stimuli (pT) during Sham stimulation was lower, and to non-target ones (pNT) was higher in trials with these task-irrelevant retro-cues compared to neutral ones (see Table 2). This suggests that task-irrelevant retro-cues may have had a marginal distracting effect. However, the data exclude that retro-cues effects could be solely attributed to distractibility, and do not completely rule out the possibility that participants processed the task-irrelevant retro-cue as if it was a neutral one. Since there was no strong effect of these task-irrelevant cues to start with (i.e. in Sham), the effect of alpha-tACS was negligible.

To find out whether testing the same group of older adults may have led to significant learning effects in the results, performance (target responses, pT) in valid trials was compared across experimental sessions in chronological order, irrespective of the stimulation received. Valid trials were used since they were not significantly modulated by any stimulation condition, therefore allowing identifying any learning effect more clearly. A Kruskal-Wallis H test showed that there was no significant difference in performance across testing sessions (χ^2_2=1.562, p=0.458), therefore excluding significant learning effects in ageing participants' performance.

Figure 6

DISCUSSION

Using brain stimulation coupled with a WM retro-cueing paradigm, we investigated whether in the ageing brain alpha oscillations may be causally linked to inhibitory abilities, namely the capacity of ignoring task-irrelevant information. We purposefully choose to experiment this causal link in the ageing brain because both these oscillations and abilities are known to deteriorate with ageing (Gazzaley et al, 2005; Hasher and Zacks, 1988; Hasher et al, 2007; Klimesch et al, 2007; Salthouse and Meinz, 1995; Vaden et al, 2012). We therefore reasoned that any alpha-tACS induced changes in inhibition may more clearly reveal a causal link between alpha oscillations and these abilities. In a pre-stimulation condition, we first established that inhibitory abilities were significantly poorer in ageing than in younger adults. To probe the possible causal link between alpha and inhibition in ageing adults, we subsequently compared parietal alpha-tAC stimulation with either no stimulations (Sham) or with two control stimulation conditions (theta and gamma tACS). Stimulation was combined with a WM retro-cueing paradigm that measures overall WM recall precision as well as the source of error in performance including indexes of inhibitory abilities, i.e. probability of target and of non-target responses (e.g. Gazzaley and Nobre, 2012; Pertzov et al, 2013).

Our analyses yielded several new findings. First, we showed that pre-stimulation there was an advantage in younger but not in older participants for valid retro-cued trials. There was also an overall cost in performing invalid retro-cued trials, which was significantly higher in older than younger participants. Specifically, older adults showed a lower probability to respond to target stimuli (smaller pT) in invalid relative to valid and neutral retro-cues, and more misbinding errors (larger probability to respond to non-target stimuli, pNT) regardless of the retro-cue, similar to previous reports (e.g. Peich et al, 2013; Pertzov et al, 2012). Remarkably, however, in absence of retro-cue (i.e. in neutral trials) ageing participants' target responses were equivalent to younger adults. Together these results indicate that ageing adults were still susceptible to the effect of retro-cues, suggesting that their memory retained some flexibility, similar to younger adults (Zokaei et al, 2014). Second, we found that relative to Sham, parietal alpha-tACS in ageing participants resulted in an increased probability of target responses, specifically in trials with invalid retro-cues.

Therefore, the cost in performance associated with invalid retro-cues was significantly ameliorated following alpha parietal-tACS, and no longer differed from younger adults. In the context of these invalid retro-cues, we also observed fewer misbinding errors after stimulation. Lastly, recall precision was significantly decreased relative to younger adults similar to previous reports (e.g. Peich et al, 2013), and changed in most of our older adults following alpha and gamma stimulation, but because of the high variability within the sample this change did not reach significance at a group level.

Older adults do not benefit from visual retro-cue

Pre-stimulation, older adults were influenced by the retro-cue but differently from younger, there was no advantage for valid trials and an enlarged cost in invalid trials (fewer target responses and increased misbinding errors respectively). Weaker performance in invalid trials may be due to impoverished re-direction of attention and reduced ability to suppress task-irrelevant information held in working memory, which are known to decline with ageing (Craik and Salthouse, 2000; Gazzaley et al, 2005; Hasher and Zacks, 1988; Hasher et al, 2007). In contrast, our younger participants showed a significant advantage, i.e. higher probability of target responses, in performing valid retro-cues consistent with previous studies (e.g. Pertzov et al, 2013). This advantage may reflect a combination of factors, such as facilitated recall, which can be initiated with the item prioritised in working memory by the retro-cue, as well as an increased robustness to interference from task-irrelevant stimuli, and extra protection of the retro-cued item from temporal decay (Pertzov et al, 2013).

Research on the role of retro-cue in ageing adults showed that this may either improve performance (Mok et al, 2016) or not (Duarte et al, 2013; Newsome et al, 2015). Methodological differences may account for this inconsistency, such as the use of binary relative to continuous, analogue responses as in our task, or the use of only valid retro-cues compared to a combination of valid and invalid retro-cues as in our experiment. Paradigms with only valid retro-cues may induce participants to 'trust' the information provided by the cue, and they also do not tax on inhibitory abilities as much as our paradigm did (see also Gazzaley and Nobre,

519 2012; Pertzov et al, 2013). These factors may explain our ageing adults' lack of advantage for valid trials
520 and the cost associated with the invalid ones. This cost in performance represents an important novelty in
521 our study as it revealed residual memory functioning and the flexibility of older adults' memory since
522 elderly performed significantly different in the valid and invalid retro-cues. Retro-cues may have also lead
523 to weaker performance because they act as distractors, and consequently diverted participants' attention
524 (Duarte et al, 2013; Healey et al, 2008; Newsome et al, 2015). However, we specifically explored this issue
525 in Experiment 3 and found that distractibility alone did not account for significant costs in performance.

526 **Cognitive and physiological changes in inhibitory abilities associated with parietal alpha-tACS**

527 Parietal alpha stimulation resulted in improved target responses, specifically in the context of invalid retro-
528 cues, and in a change in misbinding errors that increased in neutral retro-cue (no retro-cue) and decreased in
529 invalid ones. Alpha oscillations are linked to inhibitory processes, such that, for instance, in young adults
530 strong alpha modulation corresponds to less interference from distractors (Bonnefond and Jensen, 2012;
531 Jensen and Mazaheri, 2010; Klimesch et al, 2007; Scheeringa et al, 2009). We therefore suggest that the
532 inhibitory nature of alpha-tACS may have suppressed the inter-stimuli conflict at encoding, whereby
533 stimuli typically compete with each other for working memory resources (Berryhill et al, 2012; Bonnefond
534 and Jensen, 2012; Desimone and Duncan, 1995), and it also attenuated the retro-cue effect. The reduction
535 of the inter-stimuli conflict at encoding may have increased the inter-stimuli interference, a change that was
536 not offset in neutral retro-cues trials. Hence this resulted in impoverished performance, i.e. fewer target
537 responses and more misbinding errors in our ageing participants. Moreover, the diminished effect of the
538 retro-cue resulted in increased target responses especially in invalid retro-cues because pre-stimulation these
539 retro-cues were associated with the largest cost in performance. Therefore, weakening the effect of these
540 cues resulted in the largest increase in target responses.

541 Evidence of the link between alpha oscillations and inhibitory abilities has so far been mainly correlational
542 and based on EEG studies (e.g. Klimesch, 2012; Jensen and Mazaheri, 2010). Recently, evidence of the

causal role of alpha in inhibition came from a tACS experiment in younger participants (Helfrich et al, 2014). Older adults allowed us to further establish the role of alpha oscillations in inhibitory abilities by showing that these oscillations continue to be causally linked to inhibition later in life. tACS has been implemented to either entrain (Ozen et al, 2010; Zaehle et al, 2010; but see Vossen et al, 2016) or desynchronize oscillatory activity (Guerra et al, 2016; Struber et al, 2014). We suggest that in our ageing participants improved inhibitory abilities following stimulation may be due to alpha-tACS amplifying neuronal activity in the fronto-parietal network based on the phenomenon of resonance (Buzsaki, 2006). Resonance entails that matching the endogenous oscillation of brain networks supporting a particular cognitive task with the frequency of tAC stimulation may result in augmenting the activity of these networks and their coherence, i.e. neuronal synchronization (Hermann et al, 2013). This is because tACS is thought to promote a wider recruitment of neurons specific for a cognitive function into rhythmically firing networks (Battleday et al, 2014; Hermann et al, 2013), which in turns is likely to result in behavioural changes in activities subserved by these neurons.

In our ageing adults, parietal alpha-tACS may have helped recruiting a larger population of neurons engaged in inhibition. By triggering a top-down mechanism that inhibited the processing of task-irrelevant information (Jensen and Mazaheri, 2010; Hanslmayr et al, 2011; Sauseng et al, 2009; Zanto & Gazzaley, 2009), alpha stimulation may in turn have significantly increased target responses and reduced misbinding errors especially in trials associated with the largest cost in performance pre-stimulation. These improvements were particularly noticeable in an ageing sample since both alpha oscillations and inhibitory abilities are impoverished (Gazzaley et al, 2005; Hasher and Zacks, 1988; Hasher et al, 2007; Klimesch et al, 2007; Salthouse and Meinz, 1995). Our data provide evidence that alpha oscillations represent a potentially viable inhibitory mechanism in the elderly, which could be reinforced via non-invasive neurostimuation. However, alternative explanations cannot be excluded, for instance that older people may compensate the alteration of alpha oscillations with other mechanisms during memory retention, which allow significant residual WM performance (Leenders et al, 2016).

Our results also showed that recall precision did not change significantly following any stimulation conditions at a group level. However, precision did improve in most ageing adults following alpha and gamma stimulation, suggesting that lack of significant group changes in this index may be due to the large individual variability in our ageing sample.

In sum, we studied whether in ageing adults alpha oscillations and inhibitory abilities are causally linked. We combined tACS with a retro-cue paradigm assessing WM and inhibitory abilities and found alpha-tACS induced improvement in both target responses and misbinding errors –two indexes of inhibitory abilities. Most ageing adults also showed a tendency to improved memory recall following alpha and gamma-tACS. We therefore concluded that in ageing alpha oscillations are causally linked to inhibitory abilities, and that despite being impoverished, these abilities can still be changed.

FIGURES AND TABLES CAPTIONS

Figure 1: The working memory retro-cueing task. Participants memorized a display of four arrow stimuli differing in orientation and colour. Following a delay period, one of the four coloured arrows reappeared in a random orientation and participants matched it as closely as possible to the original orientation. In 70% of the trials during the delay in Experiment 1 and 2, a coloured cue was presented which highlights an item that was more likely to be later probed. In these trials, the probe either matched the cued items (validly cued trials, *N*=56) or it did not (invalidly cued trials, *N*=28). In the remaining 30% of the trials (*N*=42), no cue was present during the delay. In Experiment 3, which aimed to test whether retro-cues may act as distracters, 30% of the trials (*N*=42) consisted of a neutral condition equivalent to the one used in Experiments 1 and 2. In the remaining 70% of the trials (*N*=84) the colour of the fixation changed into a colour that was never part of the stimulus display, i.e. pink (task-irrelevant cueing condition).

Figure 2: Experimental design. In Experiment 1, younger and older participants performed the working memory retro-cueing task in a pre-stimulation session with no tACS (baseline). In Experiment 2, older participants only performed the same task while receiving 20 minutes of bilateral parietal (P3 and P4 on 10-20 EEG system) tACS stimulation at either 4Hz (**Θ** band), 10Hz (**α** band), 35Hz (**γ** band), or Sham. The order of the stimulation conditions was counterbalanced and pseudo-randomized across participants, with testing sessions at least 48-hours apart.

Figure 3: Probability of target responses in Experiments 1 and 2. (A) Performance at pre-stimulation (baseline) in younger and older adults, and (B) changes following alpha, gamma, theta-tACS and Sham in older participants only in valid, invalid and neutral retro-cues. Each dot indicates a participant's performance in each condition. Cross symbols refer to the group mean, and bold lines to the comparisons most relevant for the study's hypotheses. Asterisks denote statistically significant differences (p<0.05).

Figure 4: Misbinding errors in Experiments 1 and 2. (A) Performance at pre-stimulation (baseline) in younger and older adults, and (B) changes following alpha, gamma, theta-tACS and Sham in older participants only in valid, invalid and neutral retro-cues. Each dot indicates a participant's performance in each condition. Cross symbols refer to the group mean, and bold lines to the comparisons most relevant for the study's hypotheses. Asterisks denote statistically significant differences (p<0.05).

Figure 5: Alpha-tACS effects in Experiments 2 relative to baseline performance. Performance in (A) target (pT) and (B) non-target responses (pNT) in invalid retro-cues following alpha-tACS as a function of baseline performance (here Sham) in older adults.

Figure 6: Results of Experiment 3. Performance changes in (A) target (pT) and (B) non-target responses (pNT) in task-irrelevant and neutral cues following alpha-tACS and Sham in ageing participants. Each dot indicates a participant's performance in each condition. Cross symbols refer to the group mean. Asterisks indicate statistically significant differences (p<0.05).

Table 1. Experiment 1 (no stimulation): accuracy (precision) and source of error (κ, pT, pNT, pU) in younger and older participants; mean with standard error in italics. Asterisks indicate statistically significant differences (p<0.05).

Table 2: Experiments 2 and 3: accuracy (precision) and source of error (κ, pT, pNT, pU) in older participants in each stimulation and retrocueing conditions; mean with standard error in italics. Asterisks indicate statistically significant differences (p<0.05).

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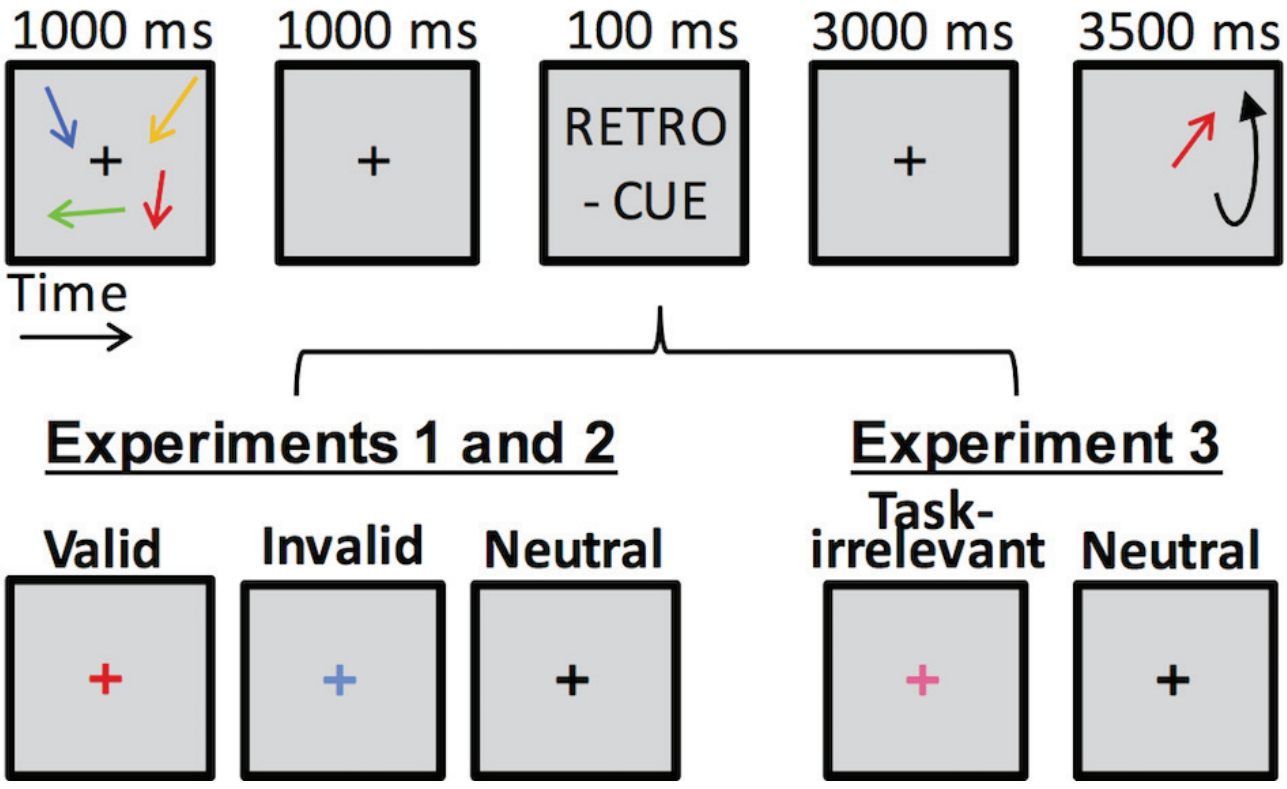

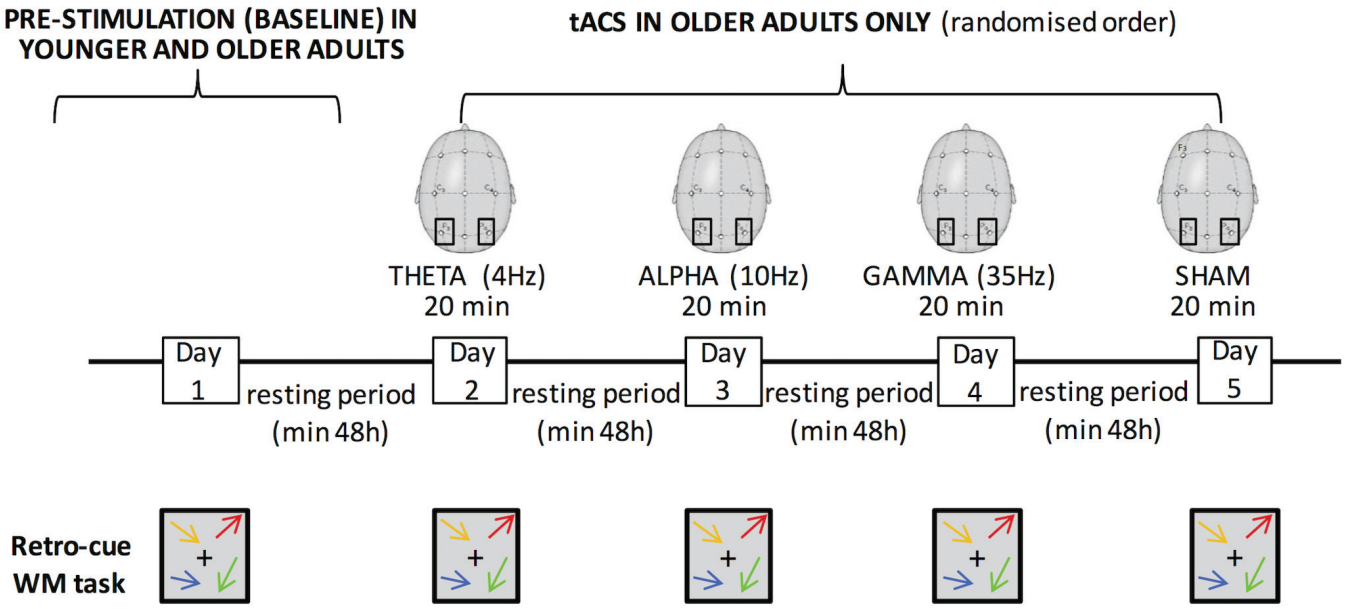

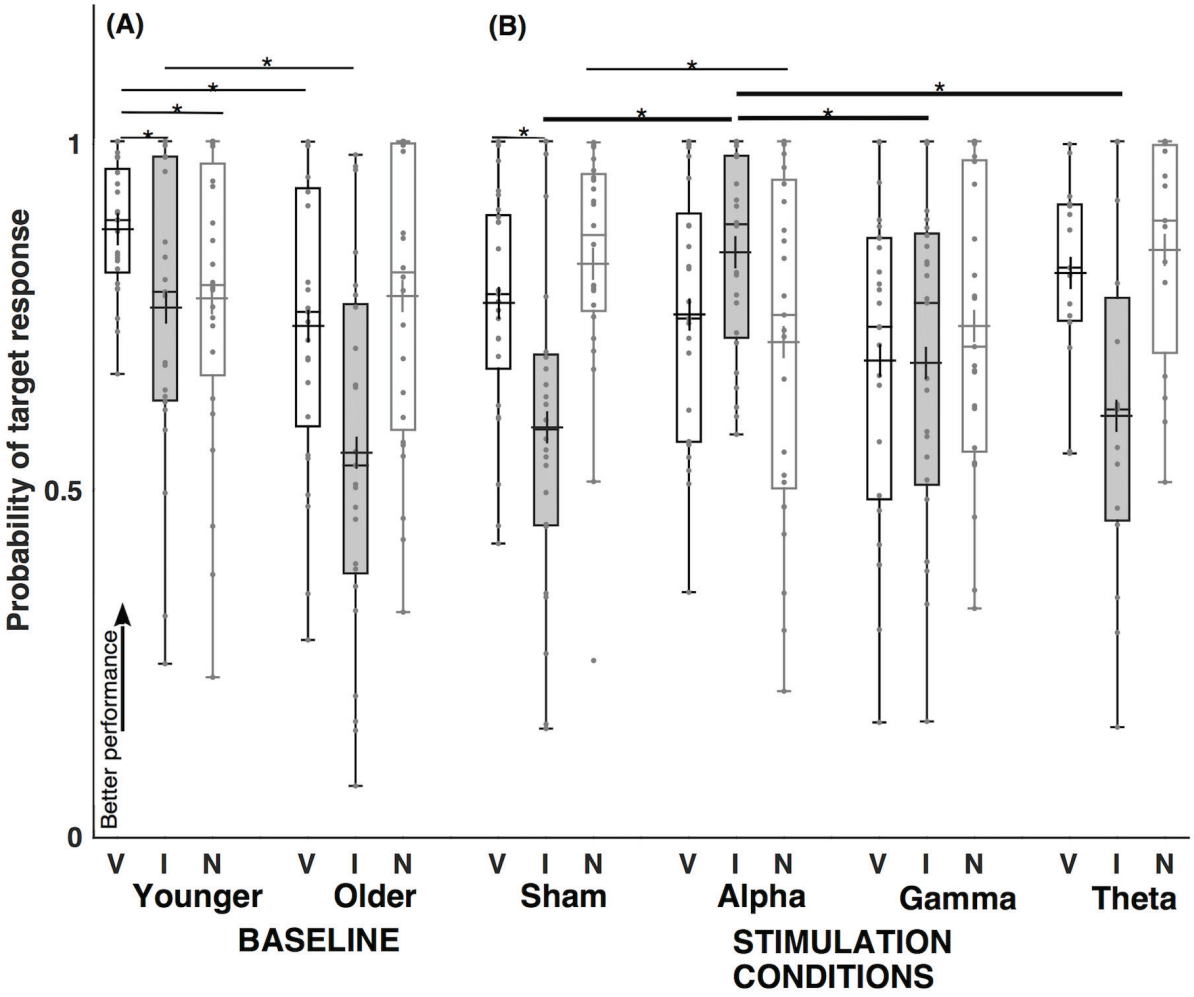

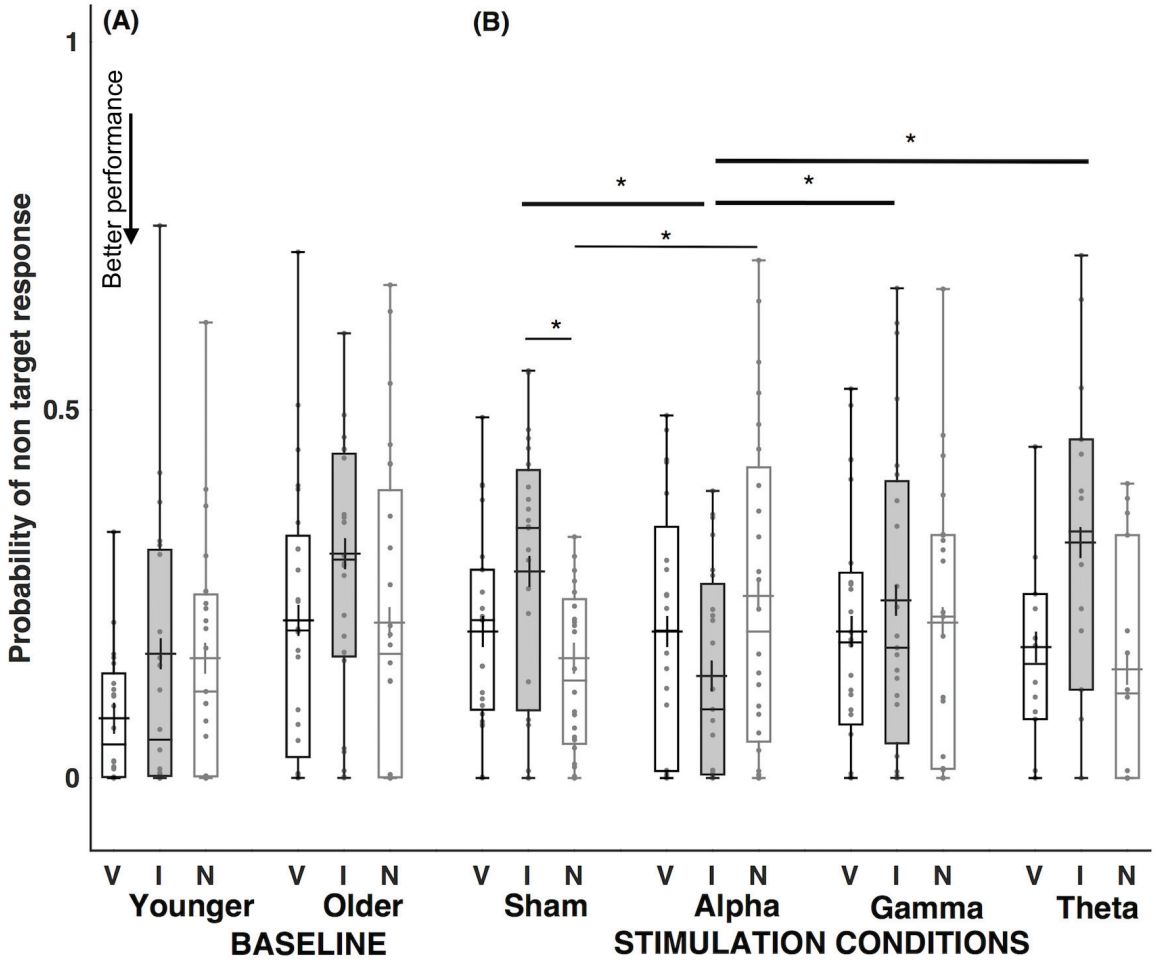

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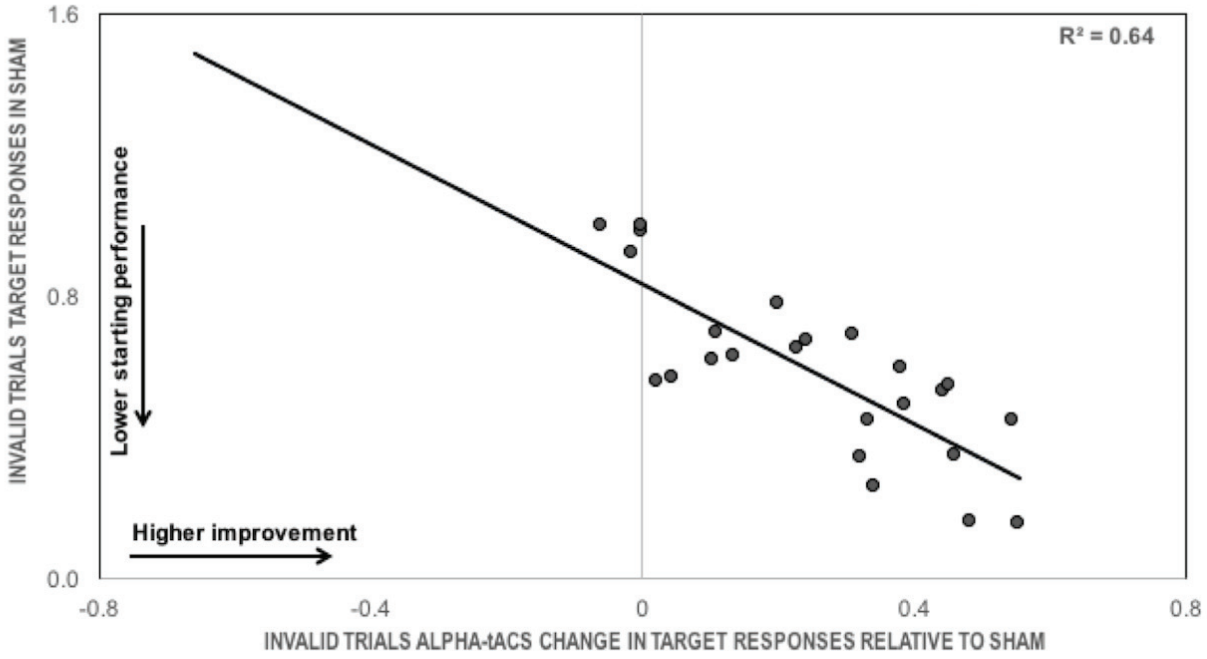

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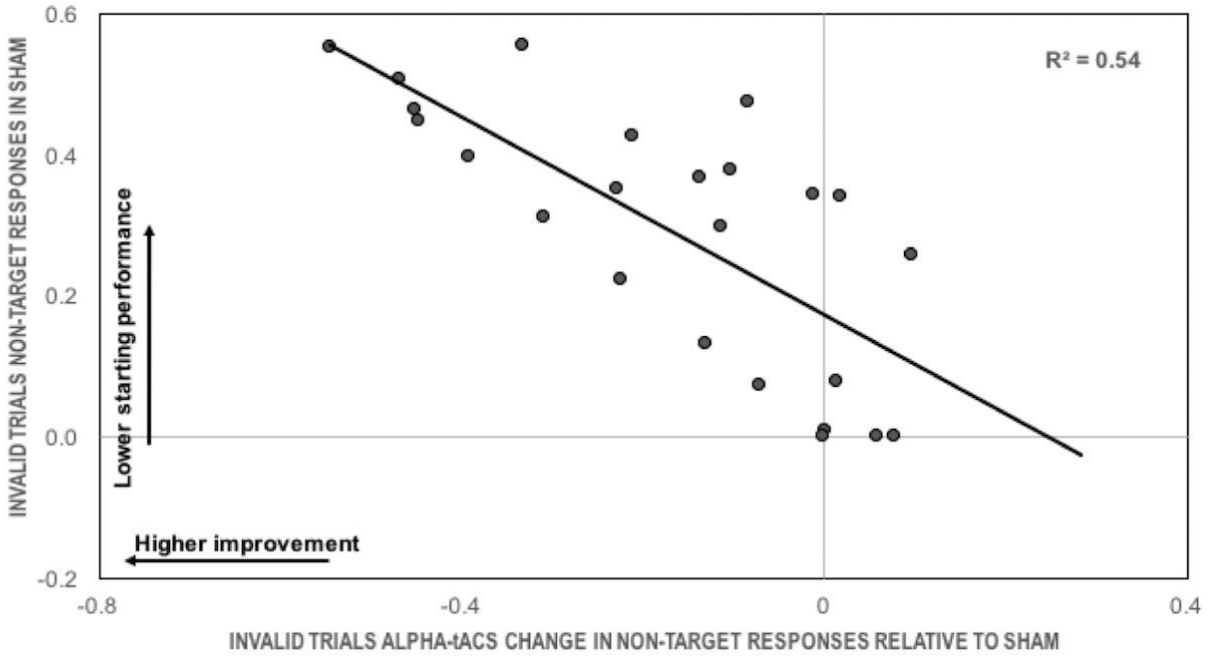

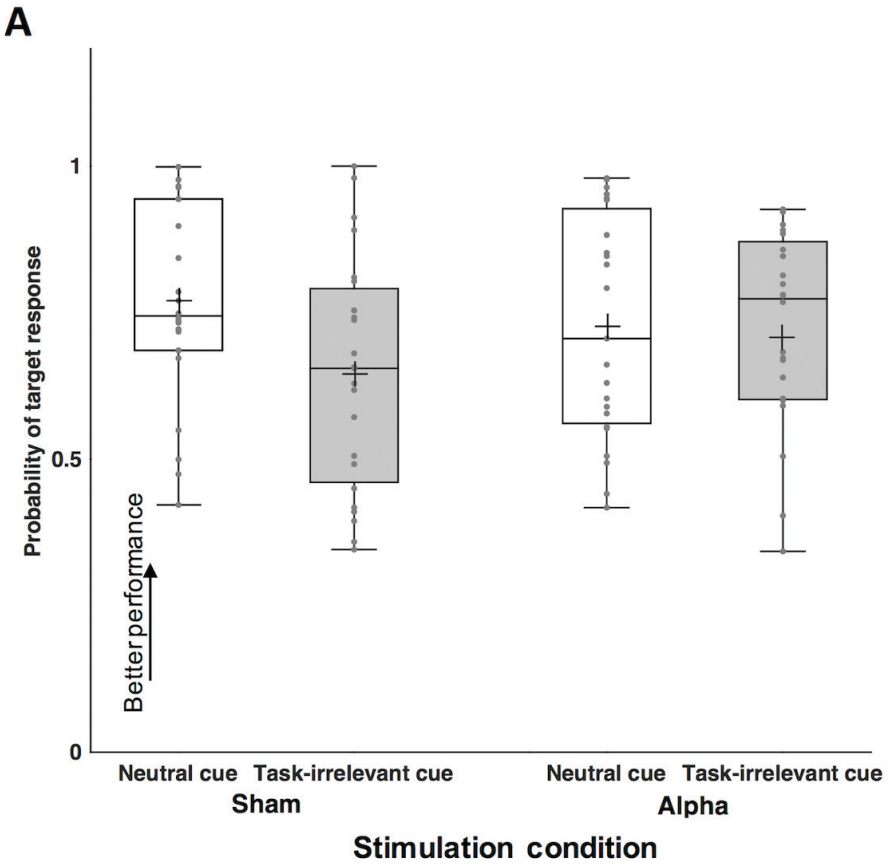

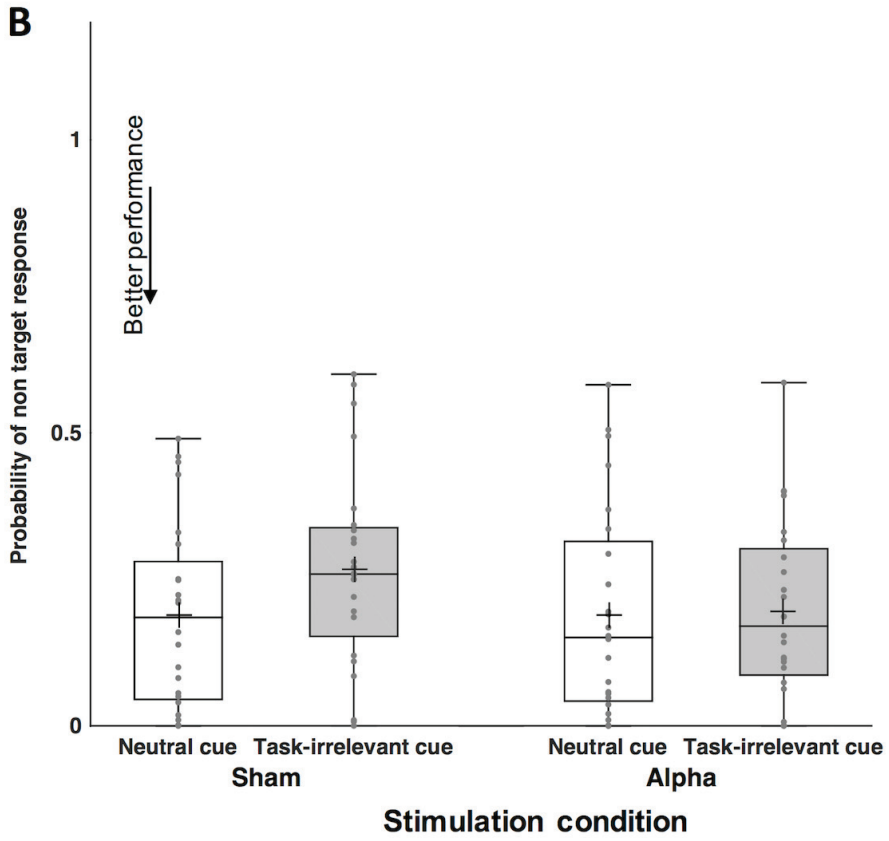

Table 1

Cueing condition	Younger participants					Older participants				
	P	κ	pT	pNT	pU	P	κ	pT	pNT	pU
All retro-cues	1.23 *0.06*	2.62 *0.25*	0.81 *0.02*	0.14 *0.03*	0.06 *0.01*	1.0* *0.02*	2.27 *0.20*	0.68* *0.03*	0.24* *0.02*	0.08 *0.02*
Valid	1.27 *0.06*	2.63 *0.24*	0.87 *0.02*	0.09 *0.02*	0.04 *0.01*	1.01* *0.03*	2.01 *0.24*	0.74* *0.04*	0.21* *0.04*	0.05 *0.03*
Invalid	1.19 *0.07*	3.42 *0.5*	0.76 *0.05*	0.18 *0.05*	0.10 *0.04*	0.97* *0.02*	3.18 *0.56*	0.55* *0.05*	0.30* *0.04*	0.15 *0.02*
Neutral	1.21 *0.06*	2.88 *0.3*	0.77 *0.04*	0.17 *0.03*	0.03 *0.01*	1.04* *0.03*	1.82 *0.15*	0.78 *0.04*	0.20* *0.04*	0.05 *0.02*

Legend:

P= precision; κ: kappa; pT: probability of target responses; pNT: probability of non-target responses (misbinding errors); pU: random error. *Indicates significant group difference (p<0.05).

Table 2

		STIMULATION CONDITION (Older participants)																			
		Sham					Alpha					Theta					Gamma				
	Cueing condition	P	κ	pT	pNT	pU	P	κ	pT	pNT	pU	P	κ	pT	pNT	pU	P	κ	pT	pNT	pU
Exp 2	All retrocues	1.11 *0.05*	2.79 *0.25*	0.72 *0.03*	0.22 *0.02*	0.07 *0.02*	1.12 *0.05*	2.52 *0.26*	0.77 *0.03*	0.19 *0.02*	0.04 *0.01*	1.08 *0.05*	2.33 *0.21*	0.75 *0.04*	0.21 *0.03*	0.03 *0.02*	1.11 *0.05*	2.50 *0.19*	0.70 *0.04*	0.21 *0.03*	0.06 *0.02*
	Valid	1.12 *0.04*	2.86 *0.46*	0.77 *0.03*	0.20 *0.03*	0.07 *0.03*	1.11 *0.05*	2.30 *0.19*	0.75 *0.04*	0.20 *0.03*	0.05 *0.02*	1.15 *0.06*	2.35 *0.28*	0.81 *0.03*	0.17 *0.04*	0.02 *0.02*	1.11 *0.05*	2.54 *0.24*	0.68 *0.05*	0.20 *0.04*	0.07 *0.03*
	Invalid	1.07 *0.05*	2.85 *0.35*	0.59 *0.05*	0.29 *0.04*	0.06 *0.03*	1.11 *0.05*	2.50 *0.32*	0.84* *0.03*	0.14* *0.03*	0.04 *0.02*	1.01 *0.06*	2.52 *0.34*	0.61 *0.06*	0.33 *0.06*	0.07 *0.05*	1.10 *0.04*	2.50 *0.32*	0.68 *0.05*	0.23 *0.04*	0.06 *0.03*
	Neutral	1.14 *0.05*	2.67 *0.30*	0.82 *0.04*	0.16 *0.03*	0.08 *0.03*	1.13 *0.05*	2.47 *0.35*	0.71 *0.05*	0.24* *0.04*	0.04 *0.02*	1.13 *0.05*	2.11 *0.22*	0.85 *0.04*	0.14 *0.04*	0.01 *0.008*	1.12 *0.05*	2.47 *0.35*	0.73 *0.04*	0.21 *0.04*	0.05 *0.03*
Exp 3	All retrocues	1.09 *0.05*	2.67 *0.23*	0.73 *0.03*	0.26 *0.02*	0.11 *0.02*	1.16 *0.06*	2.86 *0.26*	0.72 *0.04*	0.22 *0.03*	0.14 *0.04*	nt									
	Task-irrelevant	1.06 *0.05*	2.41 *0.15*	0.67 *0.04*	0.29 *0.03*	0.12 *0.03*	1.14 *0.06*	2.92 *0.38*	0.73 *0.04*	0.22 *0.03*	0.13 *0.07*										
	Neutral	1.11 *0.05*	2.93 *0.41*	0.78 *0.03*	0.22 *0.03*	0.09 *0.03*	1.18 *0.07*	2.79 *0.27*	0.71 *0.05*	0.22 *0.04*	0.15 *0.04*										

Legend: Exp= experiment; P= precision; κ: kappa; pT: probability of target responses; pNT: probability of non-target responses (misbinding errors); pU: random error; nt= not tested as not part of the planned investigation. *Indicates significant difference from Sham (p<0.05).